Cardiovascular Diabetology

RESEARCH

Open Access

Joint association of urinary albumin-to-creatinine ratio within normal range and triglyceride-glucose index with incident cardiovascular disease: a prospective cohort study

Du Fengjun[1], Tang Junli[2], Lu Zilong[2], Chen Xiaorong[3], Zhang Jiyu[2], Xu Jianwei[3], Zhang Binyin[2], Dong Jing[2], Ren Jie[2], Xu Chunxiao[2], Gao Congcong[2], Guo Xiaolei[2*], Wu Jing[3*] and Ma Jixiang[4*]

Abstract

Background Elevated urinary albumin-to-creatinine ratio (UACR) within the normal range (< 30 mg/g) and the triglyceride-glucose (TyG) index are associated with cardiovascular disease (CVD) incidence, yet their joint effect remains underexplored.

Methods This prospective cohort study used data from the 2016 Shandong-MOH Salt and Hypertension (SMASH) project, linked to CVD records until September 30, 2023, including 14,481 adults with normal UACR. Participants were stratified by TyG index and UACR quantiles. Multivariable Cox proportional hazards models and restricted cubic splines (RCS) were employed to evaluate individual and joint effects on overall CVD, coronary heart disease (CHD), and stroke. The incremental predictive value was assessed using the C-index, Net Reclassification Improvement (NRI), and Integrated Discrimination Improvement (IDI). Additionally, an exploratory mediation analysis was performed to examine the potential bidirectional effects between the TyG index and UACR.

Results Mean age was 41.75 ± 13.06 years, with median follow-up of 7.2 years. Among 420 incident overall CVD cases (309 stroke, 111 CHD), Compared to the Low TyG & Low UACR group, the High TyG & High UACR group demonstrated the highest risks for overall CVD (HR = 2.632, 95% CI: 1.695–4.085, $P < 0.001$), CHD (HR = 2.680, 95% CI: 1.144–6.282, $P = 0.023$), and stroke (HR = 2.628, 95% CI: 1.573–4.392, $P < 0.001$). The TyG index showed nonlinear associations with overall CVD and stroke risk but a linear association with CHD, while UACR exhibited linear positive correlations with all outcomes. The model combining the TyG index and UACR significantly enhanced the predictive ability for CVD

*Correspondence:
Guo Xiaolei
guoxiaolei@126.com
Wu Jing
wujing@ncncd.chinacdc.cn
Ma Jixiang
majix@163.com

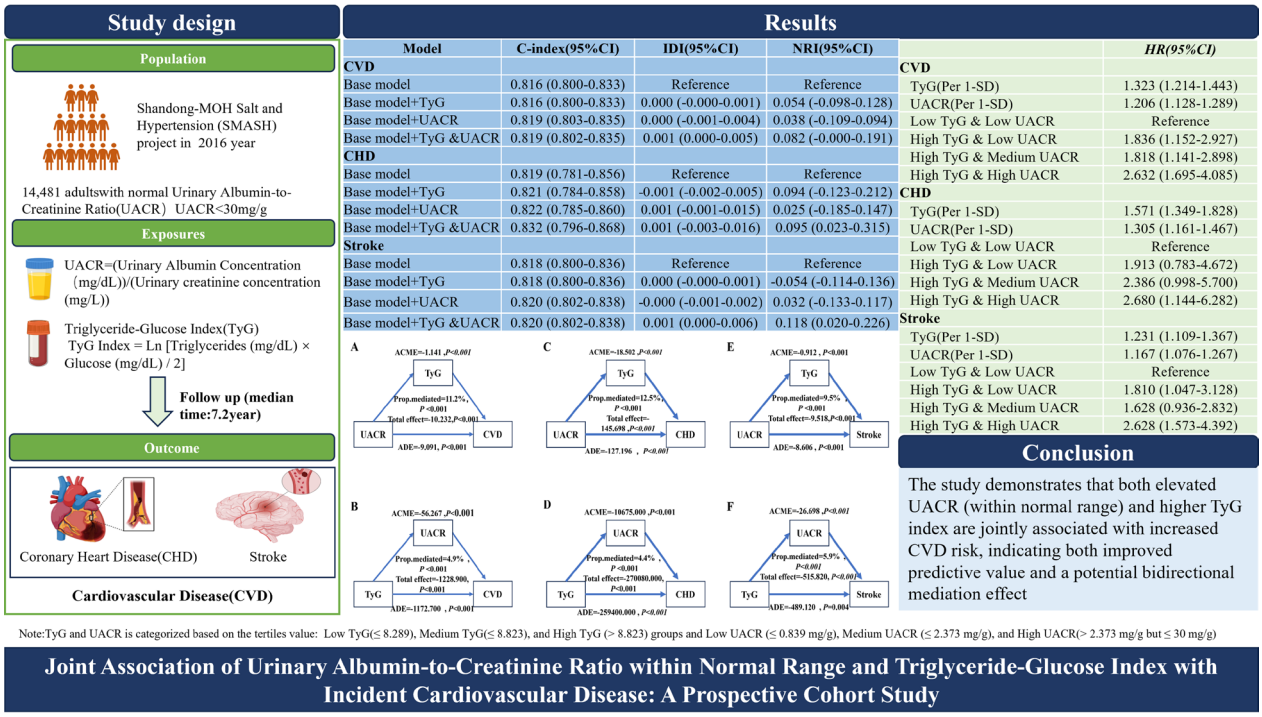
Full list of author information is available at the end of the article

events. Mediation analysis revealed that elevated UACR significantly mediated 4.9% of the association between TyG index and CVD, while elevated TyG index mediated 11.2% of the association between UACR and CVD.

Conclusion The study demonstrates that both elevated UACR (within normal range) and higher TyG index are jointly associated with increased CVD risk, with evidence suggesting potential bidirectional mediation. Their combined assessment provides significant incremental predictive value, supporting its integration into high-risk population screening for precise CVD prevention and management.

Keywords Triglyceride-glucose (TyG) index, Insulin resistance, Urinary albumin-to-creatinine ratio(UACR), Cardiovascular disease

Graphical abstract



Research insights

What is currently known about this topic?

- Urinary albumin-to-creatinine ratio(UACR) within the normal range is associated with CVD.
- Triglyceride-glucose index(TyG) is a biomarker for CVD.
- There is a lack of research evidence on the joint effect of both on cardiovascular disease in populations with a normal UACR.

What is the key research question?

- What is the joint association of UACR within the normal range and TyG index with the incidence of CVD?

What is new?

- An increase in UACR within the normal range is linearly associated with the incidence of CVD.
- TyG index and UACR have a joint effect on CVD, with high-normal UACR (>2.373 mg/g but ≤ 30 mg/g) and high TyG index (>8.823) being associated with the highest risk of CVD. The model combining the TyG index and UACR significantly enhanced the predictive ability for CVD.
- TyG index and UACR within the normal range may exert mutual mediation on the incidence of CVD.

How might this study influence clinical practice?

- The joint use of UACR and TyG index may serve as an important indicator for precise prevention and stratified management of CVD in populations with normal UACR.

Introduction

Cardiovascular diseases (CVDs) are a leading global cause of mortality and disease burden, accounting for approximately 17.9 million deaths annually. Heart attacks and stroke contribute to up to 80% of these deaths [1]. In China, CVDs account for more than 40% of total deaths, and the burden continues to grow due to persistent risk factors [2]. Although traditional risk factors such as age, hypercholesterolemia, and hypertension are used for risk assessment, approximately one-third of cardiovascular events occur in individuals classified as low-risk [3], underscoring the urgent need for novel risk markers and interventional targets.

The urine albumin-to-creatinine ratio (UACR) is a sensitive marker of renal and vascular endothelial function and plays a critical role in the early diagnosis of chronic kidney disease (CKD) [4]. Typically, UACR ≥ 30 mg/g defines kidney injury and is also recognized as a significant CVD risk factor [5]. In 2021, the European Society of Cardiology (ESC) recommended incorporating albuminuria and estimated glomerular filtration rate (eGFR) into routine CVD prevention assessments [6]. However, studies indicate that even within the normal range (UACR < 30 mg/g), elevated levels remain associated with increased CVD risk, with a linear relationship between UACR and CVD mortality observed starting from as low as 1 mg/g [7–9]. Nevertheless, research on the impact of lower UACR levels on the incidence and mortality of new CVDs is still limited. Therefore, further exploration is needed on how to identify and manage CVD risk within the traditional normal range of UACR.

Insulin resistance (IR), which refers to reduced sensitivity to insulin-mediated glucose clearance, is an independent risk factor for both CVD and CKD, involving multiple organs and metabolic pathways [10, 11]. The gold standard for assessing IR is the high insulin-normal glucose clamp test, but due to its high cost and invasiveness, it is not suitable for routine clinical use [12]. An alternative method, the Homeostasis Model Assessment (HOMA), is less accurate for individuals who have received insulin treatment or have lost β-cell function [13]. The triglyceride-glucose (TyG) index, as an effective and convenient clinical surrogate marker, has been widely used in research and epidemiological studies and has been shown to be associated with the incidence, mortality of CVD, and the development of CKD [14–19].

There is a close physiological and pathological link between renal function indicators and IR. The TyG index serves as a practical surrogate marker for IR, reflecting the body's state of metabolic dysregulation [20], while the UACR acts as a sensitive indicator of microvascular endothelial function [21]. Even high-normal values of UACR often suggest early vascular injury. Mechanistically, these two markers are interconnected through "microvascular endothelial dysfunction," forming a bidirectional, self-reinforcing pathological cycle: IR can induce endothelial dysfunction and glomerular injury, while microvascular damage may, in turn, exacerbate IR, collectively driving the process of atherosclerosis [21–25]. This theoretical relationship provides a crucial foundation for investigating the synergistic role of the TyG index and UACR in the development of CVD. However, existing research has predominantly focused on populations with established renal impairment. For instance, evidence suggests that decreased eGFR may mediate the effect of the TyG index on CVD [18], and IR can influence the prognosis of patients with diabetic kidney disease by promoting proteinuria [26]. In contrast, studies on populations with UACR within the normal range remain limited [27–29], and the interaction between the TyG index and UACR, as well as their combined impact on CVD incidence, is poorly understood. The potential synergistic value of these two markers in early risk assessment has yet to be clarified.

Therefore, this study utilizes data from the 2016 Shandong-Ministry of Health Action on Salt and Hypertension (SMASH) cohort. It aims to systematically analyze the combined effect of the TyG index and UACR on incident CVD, coronary heart disease (CHD), and stroke in a population with normal UACR levels, and to assess their incremental predictive value beyond established risk factors. Furthermore, it seeks to explore the potential bidirectional mediating effects between these two markers, thereby providing scientific evidence for early risk identification and targeted prevention of CVD.

Methods

Data source

This prospective cohort study utilized data from the 2016 SMASH project as the baseline [30], linked to CVD incidence monitoring data and cause-of-death monitoring data from the Shandong Chronic Disease Surveillance System for the follow-up outcomes. The SMASH project, conducted in June-July 2016, selected residents aged 18–69 years from across Shandong Province. The survey included a comprehensive range of assessments, such as questionnaires, physical measurements (height, weight, blood pressure, etc.), blood glucose, blood lipids, and other laboratory tests. A total of 16,488 participants were involved. Detailed information from the survey has been reported in other publications. The Shandong Chronic Disease Surveillance System covers all counties (cities and districts) in the province, collecting data on CVD incidence and cause of death. All data were directly reported online by trained medical institutions at various levels, with the disease prevention and control centers at each level responsible for verifying and correcting the data, ensuring a rigorous quality control process.

CVD incidence monitoring reports essential information, including the onset time, diagnosis date code, diagnosis, and diagnostic criteria. The cause-of-death monitoring provides data on the underlying cause of death and related coding. Baseline and follow-up data were matched using participants' ID numbers, with the follow-up period concluding on September 30, 2023. Prior to participation, all participants provided informed consent. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Preventive Medicine Ethics Committee of the Shandong Provincial Center for Disease Control and Prevention (approval number: 2016-7, approval date: April 29, 2016).

Study population

The initial study population was derived from the SMASH (2016) study, comprising 16,488 participants. The final analytical sample was selected based on the following criteria. Specifically, we included participants who were aged 18 years or older at baseline, had complete data for the TyG index and UACR, possessed normal baseline UACR levels, and provided complete data for all key covariates. Conversely, those with a pre-existing diagnosis of cardiovascular disease at baseline were excluded. Following this screening process (detailed in Fig. 1), a total of 14,481 participants were included in the final analysis.

Assessment of TyG and UACR

Blood samples were collected from participants at baseline who had fasted for more than 8 h, followed by centrifugation to obtain the supernatant, which was stored at -20 °C. Fasting blood glucose (FPG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using the AU480 automatic biochemical analyzer, with quality control procedures rigorously applied. The TyG index was calculated using the following formula [16]:

$$TyG = \ln\left[\frac{\mathrm{TG}\ \left(\frac{\mathrm{mg}}{\mathrm{dL}}\right) \times\ \mathrm{FPG}\ \left(\frac{\mathrm{mg}}{\mathrm{dL}}\right)}{2}\right]$$

Morning urine samples were collected from participants' first void of the day, midstream, and stored at -20 °C until analysis in the laboratory. Urinary creatinine was measured with the picric acid (Jaffe) method using the Cobas C501 analyzer, and urinary albumin was measured using solid-phase fluorescent immunoassay respectively. The UACR was calculated using the following formula [5]:

$$UACR = \frac{\text{Urine Albumin Concentration}\ \left(\frac{\mathrm{mg}}{\mathrm{dL}}\right)}{\text{Urine Creatinine Concentration}\ \left(\frac{\mathrm{mg}}{\mathrm{L}}\right)}$$

UACR ≤ 30 mg/g was defined as the normal level. In addition to treating TyG index and UACR as continuous variables, this study also categorized them into Low (≤ 8.289), Medium (≤ 8.823), and High TyG (> 8.823) groups and Low (≤ 0.839 mg/g), Medium (≤ 2.373 mg/g), and High UACR(> 2.373 mg/g but ≤ 30 mg/g) based on their respective tertiles.

Assessment of outcomes

The primary outcome of this study was the incidence of overall CVD (including CHD and stroke) among the study participants. The follow-up period for each participant was from the completion of the baseline survey until the occurrence of the first event of CHD or stroke, death, or September 30, 2023, whichever occurred first. The date of onset and death were obtained from the Shandong Chronic Disease Surveillance System. In cases where CVD incidence was not recorded but cardiovascular-related death occurred, CVD incidence was inferred from the cardiovascular mortality data, with the date of death being considered as the date of onset. The occurrence of overall CVD was classified according to the International Classification of Diseases, 10th edition (ICD-10) codes, where I20-I25 corresponds to CHD and I60-I64 corresponds to stroke.

Covariates

In this study, we considered baseline potential covariates, including age (years), gender, income level, city, region, marital status, educational level, smoking, drinking, physical activity, diet, family history of cardiovascular disease, BMI groups, hypertension [31], diabetes [32], dyslipidemia [33], central obesity [33], and eGFR [34]. Detailed definitions for all variables are provided in Table S1.

Statistical analysis

The baseline characteristics of the study participants were described according to the occurrence of CVD. Continuous variables with normal distribution were expressed as mean (standard deviation, SD), while non-normally distributed variables were presented as median (interquartile range, IQR). Categorical variables were represented as number (percentage, %). Between group comparisons were performed using t-tests, Kruskal-Wallis rank-sum tests, or Pearson Chi-square tests. Additionally, study participants were stratified into three groups based on the tertiles of the TyG index and UACR, respectively. The TyG index and UACR were then combined to form nine distinct groups. For comparisons of baseline characteristics among these nine groups, analysis of

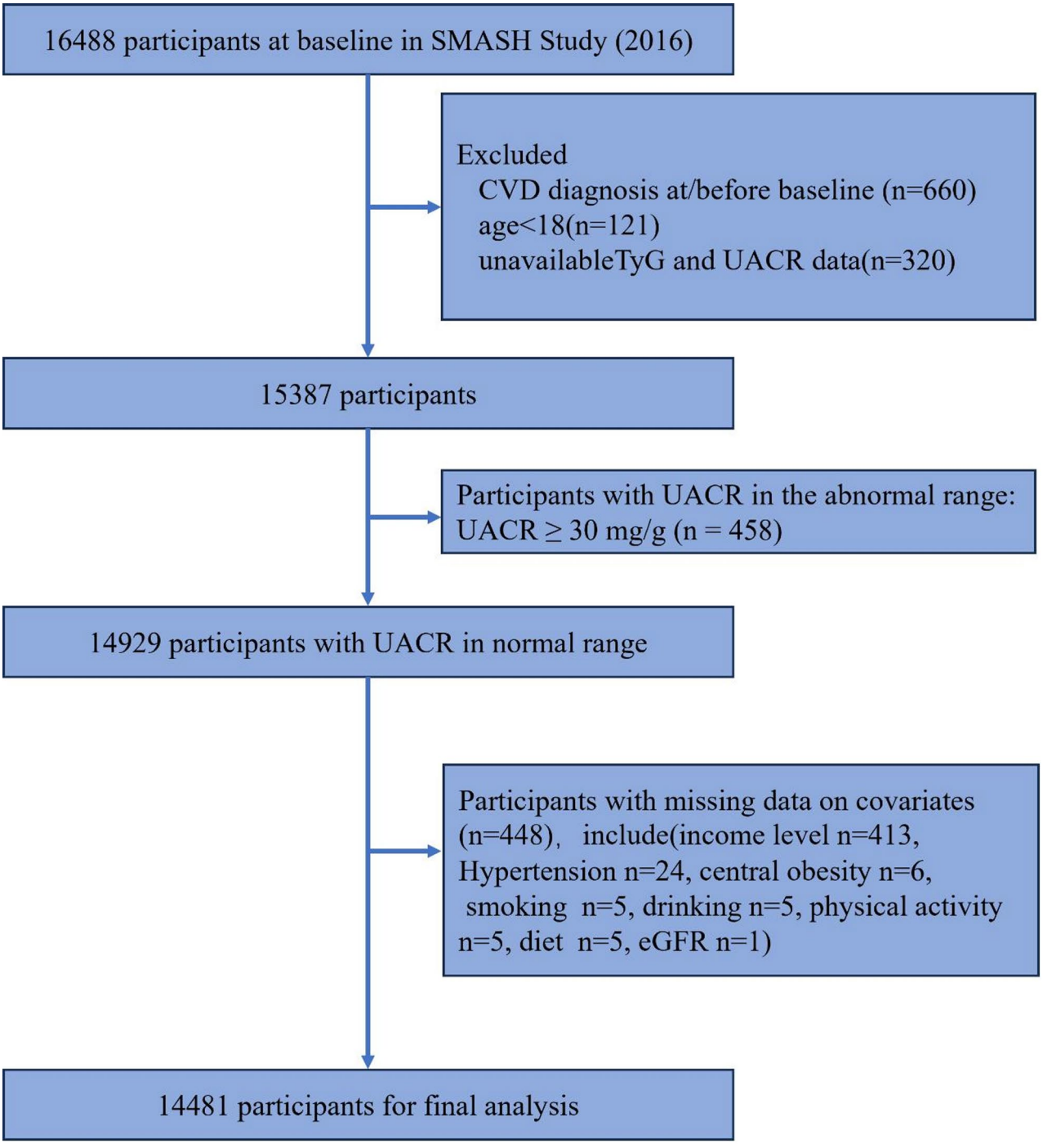


Fig. 1 Flowchart of participants selection TyG: triglyceride glucose; UACR: urinary albumin-to-creatinine ratio; CVD: cardiovascular disease, eGFR: estimated glomerular filtration rate; There are individuals with multiple missing covariates

variance (ANOVA) was used for continuous variables, while the same statistical tests as mentioned previously were applied for categorical variables.

Kaplan-Meier curves stratified by TyG index tertiles, UACR tertiles, and their combination (nine groups), with log-rank tests used to compare the cumulative hazard of each study outcome. Multivariable Cox proportional hazards models were employed to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the associations between TyG index and UACR with CVD incidence in participants with normal UACR. The analysis encompassed four approaches: (1) evaluating per 1-standard deviation (SD) increase in each index; (2) comparing extreme tertiles; (3) conducting stratified

analyses across tertiles of one marker within strata of the other; and (4) assessing their joint effects using combined tertile groups, with the Low TyG & Low UACR group as the reference. The proportional hazards assumption for the models was tested using Schoenfeld residuals. Model 1 was unadjusted model, while Model 2 was adjusted for age, gender, income level, city, region, marital status, and educational level. Model 3 was further adjusted for smoking, drinking, physical activity, diet, and family history of cardiovascular disease. The selection of covariates was based on previous studies, and the rationale is provided in Table S2.

Furthermore, restricted cubic splines (RCS) models with three knots (at the 10th, 50th, and 90th percentiles) were applied to examine potential nonlinear associations of continuous TyG index and UACR with CVD events. The likelihood ratio test was used to assess nonlinearity by comparing models with linear and spline terms, and the corresponding HRs and 95% CIs were calculated based on these knot locations.

To further evaluate the joint effects of TyG and UACR on CVD events, we restricted our analysis to the highest and lowest tertiles of both the TyG index and UACR, excluding the intermediate groups. Interaction effects were assessed on both multiplicative and additive scales [35]. Multiplicative interaction was evaluated using likelihood ratio tests, while additive interaction was assessed through three metrics: the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (SI). In the absence of additive interaction, the confidence intervals for RERI and AP would include 0, while the confidence interval for SI would include 1.

For predictive performance evaluation, a baseline prediction model was established using conventional risk factors from the SCORE2 algorithm [15], including age, gender, systolic blood pressure, smoking, total cholesterol, and HDL-C. To evaluate the incremental prognostic value, we constructed additional models by separately adding the TyG index, UACR, and their combined variable to the baseline model. Improvement in predictive performance was assessed using the C-index, integrated discrimination improvement (IDI), and net reclassification improvement (NRI) [36].

In subgroup analyses, we repeated the primary analysis using TyG & UACR combinations stratified by gender, age, smoking, drinking, physical activity, hypertension and diabetes, and explored potential modifying effects by testing interaction terms.

To confirm the robustness of our results, several additional analyses were conducted. First, to account for the impact of kidney function and other potential mediator factors on the outcomes, we further adjusted for eGFR or additional metabolic parameters (including BMI, hypertension, diabetes, dyslipidemia, and central obesity) respectively based on Model 3. Second, to minimize potential reverse causality, we excluded participants who had experienced the corresponding outcomes within the first 2 years of follow-up. Third, to address the competing risk of death, we re-analyzed the data using Fine-Gray competing risk models. In these models, the competing event was defined as death from non-CHD and non-stroke causes for the overall CVD endpoint, and as death from causes other than the disease of interest for disease-specific endpoints. Finally, E-values were calculated to quantitatively assess the potential impact of unmeasured confounding [37].

An exploratory mediation analysis was performed to assess the possible mediating role of UACR in the relationship between the TyG index and CVD events, and to quantify the mediation proportion. Specifically, TyG was used as the predictor variable, UACR as the mediator, and CVD events as the outcome variable, with adjustments made for the covariates in model 3. Additionally, the mediation effect of the TyG index on CVD events through UACR was assessed in a similar manner.

A two-sided P value < 0.05 was considered statistically significant. All statistical analyses were conducted using R software (version 4.4.0, *R* Foundation for Statistical Computing).

Results

Baseline characteristics of study participants

In this study, we included 14,481 participants (UACR $\leq$ 30 mg/g) with an average age of 41.75 years, and 49.7% were men. The median follow-up time was 7.2 years, during which 420 participants developed CVD. Table 1 shows the baseline characteristics of the participants, grouped by whether they developed CVD during follow-up. Compared to those without CVD, participants who developed CVD were older, had higher rates of smoking, drinking, hypertension, diabetes, and dyslipidemia, and had higher levels of UACR and TyG index. Additionally, when participants were divided into nine groups by tertiles of the TyG index and UACR, those in the highest joint category (High TyG & High UACR) were older and exhibited a significantly greater incidence of composite CVD, CHD, and stroke than other joint categories (Table S3) .

Association of TyG index and UACR with CVD

Kaplan-Meier curves showed a significantly higher cumulative risk of CVD in the higher TyG group (all Log-rank $P < 0.001$, Fig.S1 A CVD-C Stroke). After full adjustment for covariates, cox regression analysis revealed that each 1-SD increase in TyG index was associated with a 32.3% higher risk of CVD (HR = 1.323, 95% CI: 1.214–1.443,$P < 0.001$), a 57.1% higher risk of CHD (HR = 1.571,

Table 1 Characteristics of study population stratified by the occurrence of cardiovascular disease

Characteristic	Total(*N* = 14481)	Occurrence of CVD		*P* value
		No(*N* = 14061)	Yes(*N* = 420)	
Age(years)	41.75 (13.06)	41.39 (12.99)	53.75 (9.18)	< 0.001
Male	7198 (49.7)	6939 (49.3)	259 (61.7)	< 0.001
Income level(yuan)				< 0.001
[0,5000]	4726 (32.6)	4538 (32.3)	188 (44.8)	
(5000,10,000]	4526 (31.3)	4410 (31.4)	116 (27.6)	
(10,000,15,000]	2006 (13.9)	1958 (13.9)	48 (11.4)	
(15,000,20,000]	1684 (11.6)	1655 (11.8)	29 (6.9)	
(20,000,Inf]	1539 (10.6)	1500 (10.7)	39 (9.3)	
Educational level				< 0.001
Primary school or lower	4276 (29.5)	4082 (29.0)	194 (46.2)	
Junior high school	6316 (43.6)	6151 (43.7)	165 (39.3)	
High school or higher	3889 (26.9)	3828 (27.2)	61 (14.5)	
Rural	10,023 (69.2)	9714 (69.1)	309 (73.6)	0.056
Region				0.066
Eastern Shandong	3633 (25.1)	3547 (25.2)	86 (20.5)	
Central Southern Shandong	5536 (38.2)	5372 (38.2)	164 (39.0)	
Northwestern Shandong	5312 (36.7)	5142 (36.6)	170 (40.5)	
Marriage	12,824 (88.6)	12,423 (88.4)	401 (95.5)	< 0.001
Smoking	4104 (28.3)	3935 (28.0)	169 (40.2)	< 0.001
Drinking	3695 (25.5)	3555 (25.3)	140 (33.3)	< 0.001
Physical activity	3091 (21.3)	3001 (21.3)	90 (21.4)	1.000
Diet				0.006
Predominantly meat-based diet	911 (6.3)	889 (6.3)	22 (5.2)	
Predominantly vegetarian diet	5933 (41.0)	5729 (40.7)	204 (48.6)	
Mixed diet (meat and vegetarian)	7637 (52.7)	7443 (52.9)	194 (46.2)	
Family history of cardiovascular disease	1965 (13.6)	1881 (13.4)	84 (20.0)	< 0.001
BMI (kg/m^2)	25.09 (4.06)	25.07 (4.07)	25.91 (3.94)	< 0.001
BMI groups				< 0.001
< 24	6080 (42.0)	5945 (42.3)	135 (32.1)	
24–28	5210 (36.0)	5044 (35.9)	166 (39.5)	
≥28	3191 (22.0)	3072 (21.8)	119 (28.3)	
Hypertension	3177 (21.9)	2929 (20.8)	248 (59.0)	< 0.001
Diabetes	1208 (8.3)	1104 (7.9)	104 (24.8)	< 0.001
Dyslipidemia	4522 (31.2)	4355 (31.0)	167 (39.8)	< 0.001
Central Obesity	6087 (42.0)	5857 (41.7)	230 (54.8)	< 0.001
TyG index	8.54 [8.16, 8.99]	8.53 [8.16, 8.98]	8.83 [8.43, 9.27]	< 0.001
UACR (mg/g)	1.44 [0.61, 3.10]	1.43 [0.60, 3.07]	1.77 [0.66, 4.59]	< 0.001
eGFR(mL/min/1.73m^2)	115.56 [107.45, 124.26]	115.90 [107.69, 124.50]	107.04 [100.43, 113.18]	< 0.001

95% CI: 1.349–1.828, $P < 0.001$), and a 23.1% higher risk of stroke(HR = 1.231, 95% CI: 1.109–1.367, $P < 0.001$). Compared with the Low TyG group, the High TyG group had a 120.6%, 143.5% and 112.8% increased risk of CVD, CHD and stroke, respectively, with HRs and 95% CIs of 2.206 (1.688–2.882), 2.435 (1.461–4.059) and 2.128 (1.554–2.913). The medium TyG group had a 48.0% and 54.8% increased risk of CVD, and stroke, respectively. However, no significant association was found with CHD incidence in model3 (Table S4). RCS analysis of the relationship between TyG index and CVD incidence revealed a nonlinear association between TyG index and CVD (Fig. 2A CVD) and stroke (Fig. 2C Stroke)(P for nonlinear = 0.007 and P for nonlinear = 0.008), with an approximate linear relationship between TyG index and CHD (P for nonlinear = 0.952) (Fig. 2B CHD).

Kaplan-Meier curves showed a higher cumulative risk of CVD, CHD, and stroke in the higher UACR group ($P < 0.001$, $P = 0.013$, and $P = 0.001$, respectively; Fig. S1 D CVD-F Stroke). Furthermore, fully adjusted cox regression models(model 3) revealed that each 1-SD increase in UACR was associated with a 20.6% higher risk of CVD (HR = 1.206, 95% CI: 1.128–1.289, $P < 0.001$), a 30.5% higher risk of CHD (HR = 1.305, 95% CI: 1.161–1.467, $P < 0.001$), and a 16.7% higher risk of stroke (HR = 1.167, 95% CI: 1.076–1.267, $P < 0.001$). However, compared to

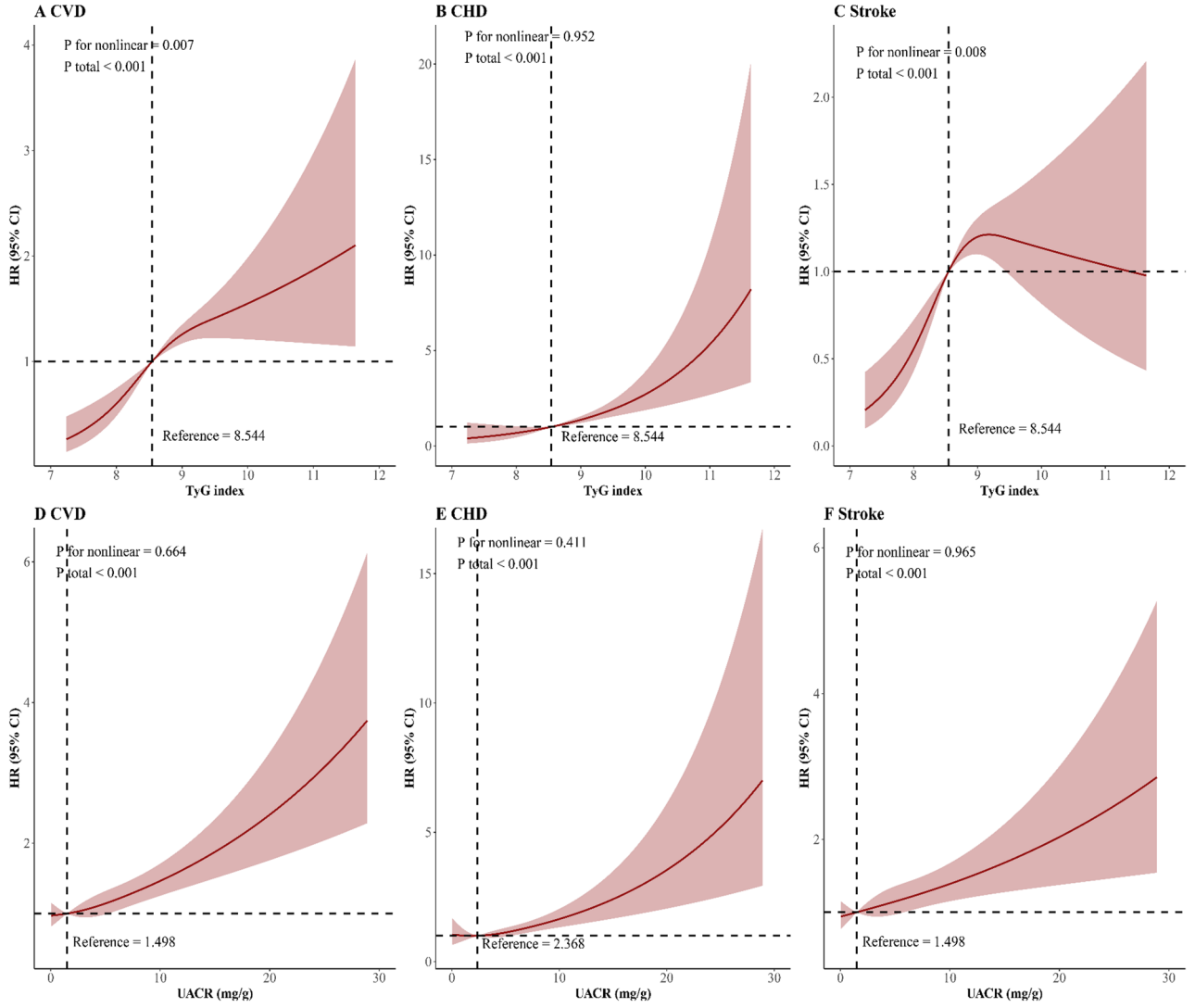


Fig. 2 Association of triglyceride glucose (TyG) index and urinary albumin-to-creatinine ratio (UACR) with the study outcomes in participants with normal UACR using restricted cubic spline models

HR: hazard ratio, CI confidence interval; TyG: triglyceride glucose; UACR: urinary albumin-to-creatinine ratio; CVD: cardiovascular disease; CHD: coronary heart disease; Models were adjusted for age, gender, income level, education level, city, region, marital status, somking, drinking, physical activity, diet, family history of cardiovascular disease. The restricted cubic spline regression models were conducted with 3 knots at the 10th, 50th, and 90th percentiles of TyG score and UACR

the Low UACR group, the High UACR group showed increased risks of CVD by 27.7% in model 3 (HR = 1.277, 95% CI: 1.011–1.612, $P = 0.040$) (Table S4). RCS regression analysis revealed a near-linear association between UACR and the incidence of CVD (P for nonlinear = 0.664), CHD (P for nonlinear = 0.411), and stroke (P for nonlinear = 0.965) (Fig. 2D CVD -F Stroke).

The joint effect analysis of the TyG index and UACR on CVD events is presented in Table S5. Across all UACR tertiles (Low UACR, Medium UACR, High UACR), a High TyG index was associated with increased risks of CVD and stroke compared to a Low TyG index. For CHD, a significant association was found only in the medium UACR group (HR = 8.916, 95% CI: 2.049–38.795, $P = 0.004$). In analyses stratified by TyG index, a High UACR significantly increased the risk of CVD (HR = 1.471, 95% CI: 1.053–2.054, $P = 0.023$) and stroke (HR = 1.485, 95% CI: 1.005–2.196, $P = 0.047$) exclusively in the High TyG group. We combined tertiles of the TyG index and UACR to form nine distinct groups. Kaplan-Meier curves demonstrated that the cumulative incidence of CVD, CHD, and stroke increased progressively across these joint TyG & UACR groups (Fig. 3; all log-rank $P < 0.001$). In the fully adjusted multivariable cox regression model (Table 2), compared to the Low TyG & Low UACR group, the High TyG & High UACR group was associated with a 163.2% increased risk of CVD (HR = 2.632, 95% CI: 1.695–4.085, $P < 0.001$), a

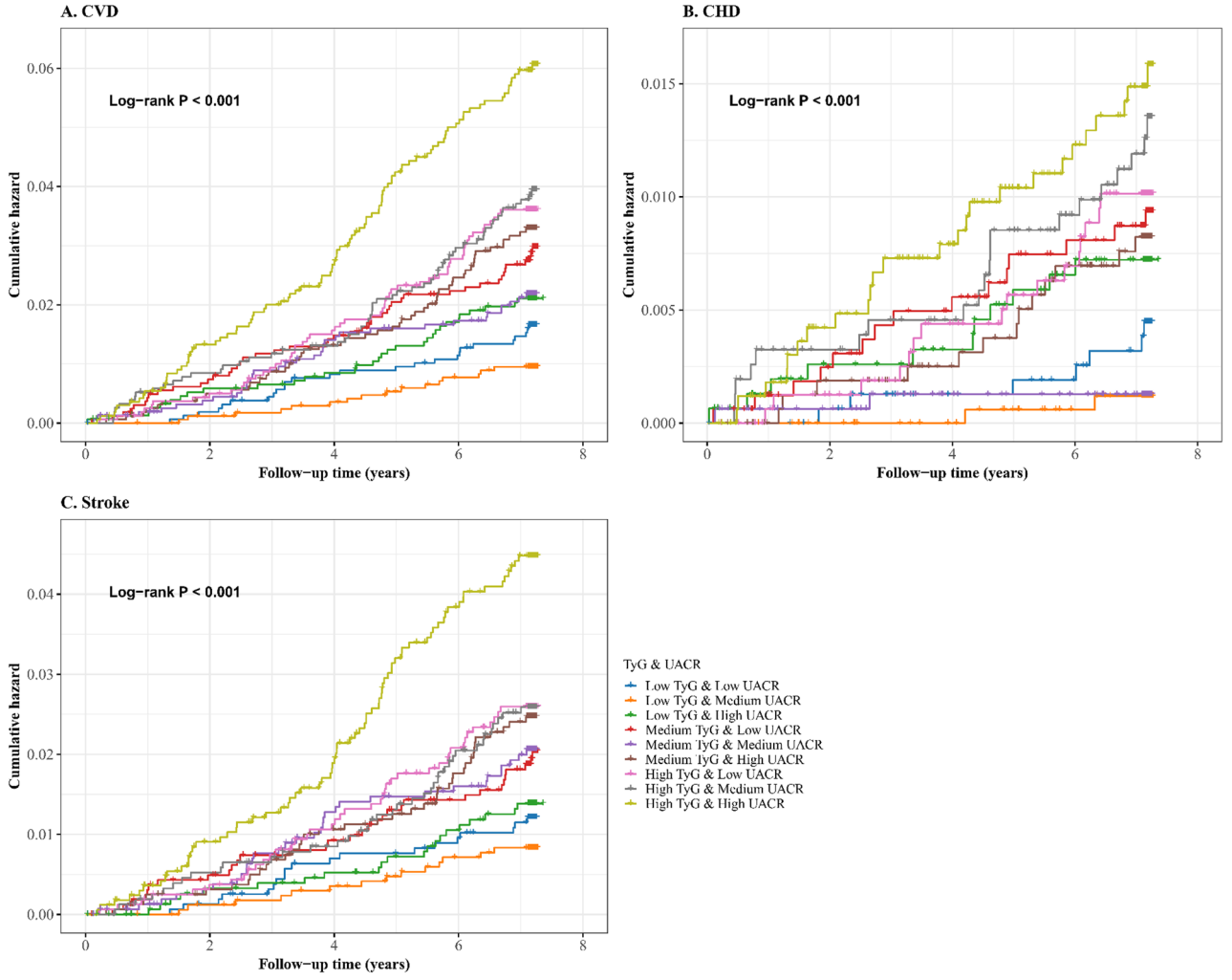


Fig. 3 Kaplan-Meier curves for cardiovascular diseases(CVD), coronary heart disease(CHD) and stroke according to triglyceride glucose (TyG) index and urinary albumin-to-creatinine ratio (UACR) combined index

TyG: triglyceride glucose index; UACR: urinary albumin-to-creatinine ratio; CVD: cardiovascular disease; CHD: coronary heart disease; TyG levels were categorized into tertiles: Low TyG (≤ 8.289), Medium TyG(≤ 8.823), and High TyG (> 8.823). UACR levels were also categorized into tertiles: Low UACR (≤ 0.839 mg/g), Medium UACR(≤ 2.373 mg/g), and High UACR(> 2.373 mg/g but ≤ 30 mg/g)

168.0% increased risk of CHD (HR = 2.680, 95% CI: 1.144–6.282, $P = 0.023$), and a 162.8% increased risk of stroke (HR = 2.628, 95% CI: 1.573–4.392, $P < 0.001$). Additionally, the High TyG & Low UACR and High TyG & Medium UACR groups were also associated with an increased risk of CVD, while the High TyG & Low UACR group was associated with an increased risk of stroke.

We then restricted our analysis to the highest and lowest tertiles of both the TyG index and UACR (excluding the intermediate groups), reclassifying these variables into binary categories (High vs. Low) to assess the multiplicative and additive interactions between them. As shown in Table S6, no significant multiplicative or additive interaction was observed for CVD, CHD, or stroke.

Incremental predictive values

We further evaluated whether the addition of TyG, UACR, and their joint indicator to the baseline model could enhance the prediction of CVD events in individuals with normal UACR. As presented in Table 3, incorporation of the combined TyG & UACR indicator significantly improved the C-index for predicting CVD, CHD, and stroke, with values of 0.819 (0.802–0.835), 0.832 (0.796–0.868), and 0.820 (0.802–0.838), respectively. These improvements in the C-index were all statistically significant compared with the baseline model ($P = 0.006$, $P = 0.006$, and $P = 0.016$, respectively). In contrast, when evaluated individually, only UACR significantly improved the C-index for predicting overall CVD. Moreover, the IDI and NRI analyses demonstrated that the combined TyG & UACR indicator

Table 2 Joint effect of the urinary albumin-to-creatinine ratio (UACR) and triglyceride glucose (TyG) index on the risks of study outcomes in participants with normal UACR

Subgroups	HR(95%CI)					
	Model 1	*P* value	Model 2	*P* value	Model 3	*P* value
CVD						
Low TyG & Low UACR	Reference		Reference		Reference	
Low TyG & Medium UACR	0.574 (0.308–1.070)	0.081	0.601 (0.322–1.123)	0.110	0.600 (0.321–1.120)	0.109
Low TyG & High UACR	1.272 (0.758–2.134)	0.362	1.325 (0.786–2.232)	0.291	1.310 (0.777–2.209)	0.310
Medium TyG & Low UACR	1.772 (1.097–2.860)	0.019	1.561 (0.966–2.521)	0.069	1.553 (0.961–2.508)	0.072
Medium TyG & Medium UACR	1.321 (0.793–2.201)	0.286	1.144 (0.685–1.912)	0.607	1.142 (0.683–1.908)	0.613
Medium TyG & High UACR	1.986 (1.240–3.180)	0.004	1.569 (0.973–2.530)	0.065	1.562 (0.968–2.519)	0.068
High TyG & Low UACR	2.175 (1.368–3.459)	0.001	1.836 (1.153–2.925)	0.011	1.836 (1.152–2.927)	0.011
High TyG & Medium UACR	2.358 (1.486–3.740)	< 0.001	1.832 (1.151–2.918)	0.011	1.818 (1.141–2.898)	0.012
High TyG & High UACR	3.646 (2.365–5.621)	< 0.001	2.648 (1.707–4.108)	< 0.001	2.632 (1.695–4.085)	< 0.001
CHD						
Low TyG & Low UACR	Reference		Reference		Reference	
Low TyG & Medium UACR	0.267 (0.055–1.285)	0.100	0.280 (0.058–1.349)	0.113	0.278 (0.058–1.341)	0.111
Low TyG & High UACR	1.627 (0.631–4.197)	0.314	1.722 (0.661–4.482)	0.266	1.659 (0.637–4.321)	0.300
Medium TyG & Low UACR	2.100 (0.856–5.150)	0.105	1.867 (0.760–4.584)	0.173	1.843 (0.750–4.526)	0.183
Medium TyG & Medium UACR	0.289 (0.060–1.391)	0.122	0.258 (0.053–1.249)	0.092	0.255 (0.053–1.231)	0.089
Medium TyG & High UACR	1.847 (0.737–4.630)	0.190	1.562 (0.615–3.967)	0.349	1.533 (0.603-3.900)	0.369
High TyG & Low UACR	2.267 (0.933–5.511)	0.071	1.921 (0.787–4.687)	0.152	1.913 (0.783–4.672)	0.155
High TyG & Medium UACR	2.971 (1.256–7.026)	0.013	2.387 (1.001–5.693)	0.050	2.386 (0.998-5.700)	0.050
High TyG & High UACR	3.494 (1.511–8.078)	0.003	2.685 (1.147–6.288)	0.023	2.680 (1.144–6.282)	0.023
Stroke						
Low TyG & Low UACR	Reference		Reference		Reference	
Low TyG & Medium UACR	0.687 (0.345–1.370)	0.287	0.721 (0.361–1.441)	0.355	0.723 (0.362–1.444)	0.358
Low TyG & High UACR	1.142 (0.614–2.124)	0.675	1.182 (0.632–2.208)	0.601	1.183 (0.633–2.212)	0.598
Medium TyG & Low UACR	1.651 (0.936–2.912)	0.084	1.454 (0.824–2.566)	0.197	1.447 (0.820–2.554)	0.203
Medium TyG & Medium UACR	1.700 (0.964-3.000)	0.067	1.458 (0.824–2.581)	0.195	1.456 (0.822–2.576)	0.197
Medium TyG & High UACR	2.037 (1.177–3.525)	0.011	1.572 (0.901–2.743)	0.111	1.570 (0.899–2.739)	0.113
High TyG & Low UACR	2.141 (1.243–3.689)	0.006	1.807 (1.047–3.120)	0.034	1.810 (1.047–3.128)	0.034
High TyG & Medium UACR	2.132 (1.232–3.690)	0.007	1.646 (0.947–2.860)	0.077	1.628 (0.936–2.832)	0.085
High TyG & High UACR	3.703 (2.233–6.138)	< 0.001	2.649 (1.586–4.425)	< 0.001	2.628 (1.573–4.392)	< 0.001

HR: hazard ratio, CI confidence interval; TyG: triglyceride glucose; UACR: urinary albumin-to-creatinine ratio; CVD: cardiovascular disease; CHD: coronary heart disease; TyG levels were categorized into tertiles: Low (≤ 8.289), Medium (≤ 8.823), and High (> 8.823). UACR levels were also categorized into tertiles: Low (≤ 0.839 mg/g), Medium (≤ 2.373 mg/g), and High (> 2.373 mg/g but ≤ 30 mg/g)

Model 1: Unadjusted; Model 2: Adjusted for age, gender, income level, education level, city, region, and marital status

Model 3: Adjusted for all variables in Model 2, plus smoking, drinking, physical activity, diet and family history of cardiovascular disease

significantly enhanced the IDI for CVD (IDI = 0.001) and stroke (IDI = 0.001), and the NRI for CHD and stroke (NRI = 0.095 and NRI = 0.118, respectively). Collectively, the joint TyG & UACR indicator provided greater incremental predictive value.

Subgroup analyses

Subgroup analyses were performed to evaluate the joint effects of TyG and UACR on CVD events across different subgroups. Compared with the Low TyG & Low UACR group, the High TyG & High UACR group was significantly associated with an increased risk of CVD and stroke in most subgroups. In the non-hypertension population, High TyG & High UACR was significantly associated with a nearly three-fold increase in CVD risk (HR = 3.937, 95% CI: 1.791–8.651) and a more than two-fold increase in stroke risk (HR = 3.277, 95% CI: 1.334–8.051). In the non-diabetic population, this combination was also associated with an approximately 1.4-fold increase in both CVD (HR = 2.365, 95% CI: 1.444–3.873) and stroke risk (HR = 2.367, 95% CI: 1.335–4.197). However, no such significant associations were observed in the hypertension or diabetic subgroups. Multiplicative interaction models further indicated no significant interactions between the joint of TyG and UACR and other variables (Tables S7, S8 and S9). It should be noted that due to the limited number of CHD cases, reliable estimates could not be obtained for some subgroups, and thus the corresponding results are not presented.

Table 3 Incremental predictive value of urinary albumin-to-creatinine ratio (UACR) and triglyceride glucose (TyG) index with risks of study outcomes in participants with normal UACR

Model	C-index(95%CI)	*P* value	IDI(95%CI)	*P* value	NRI(95%CI)	*P* value
CVD						
Base model	0.816 (0.800–0.833)		Reference		Reference	
Base model + TyG	0.816 (0.800–0.833)	0.660	0.000 (-0.000–0.001)	0.557	0.054 (– 0.098–0.128)	0.873
Base model + UACR	0.819 (0.803–0.835)	0.020	0.000 (– 0.001–0.004)	0.759	0.038 (– 0.109–0.094)	0.486
Base model + TyG &UACR	0.819 (0.802–0.835)	0.006	0.001 (0.000–0.005)	0.030	0.082 (– 0.000–0.191)	0.052
CHD						
Base model	0.819 (0.781–0.856)		Reference		Reference	
Base model + TyG	0.821 (0.784–0.858)	0.416	– 0.001 (– 0.002–0.005)	0.895	0.094 (– 0.123–0.212)	0.384
Base model + UACR	0.822 (0.785–0.860)	0.168	0.001 (– 0.001–0.015)	0.533	0.025 (– 0.185–0.147)	0.759
Base model + TyG &UACR	0.832 (0.796–0.868)	0.006	0.001 (– 0.003–0.016)	0.276	0.095 (0.023–0.315)	0.024
Stroke						
Base model	0.818 (0.800–0.836)		Reference		Reference	
Base model + TyG	0.818 (0.800–0.836)	0.562	0.000 (– 0.000–0.001)	0.537	– 0.054 (– 0.114-0.136)	0.691
Base model + UACR	0.820 (0.802–0.838)	0.136	– 0.000 (-0.001–0.002)	0.945	0.032 (– 0.133–0.117)	0.456
Base model + TyG &UACR	0.820 (0.802–0.838)	0.016	0.001 (0.000–0.006)	0.020	0.118 (0.020–0.226)	0.026

Basic models were adjusted for age, gender, BMI, SBP, hypertension medication, diabetes, total cholesterol, HDL-C. CI: confidence interval; TyG: triglyceride glucose; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol ; NRI: net reclassification index, IDI integrated discrimination improvement index; UACR: urinary albumin-to-creatinine ratio; CVD: cardiovascular disease; CHD: coronary heart disease;

Sensitivity analyses

Multiple sensitivity analyses were conducted to assess the robustness of the primary findings (Tables S10, S11 and S12). First, after further adjustment for eGFR on the basis of Model 3, the joint associations of TyG and UACR with CVD, CHD, and stroke remained consistent with the main results. However, after additional adjustment for potential mediating factors—including BMI, hypertension, diabetes, dyslipidemia, and central obesity—although the overall strength of the associations was attenuated, the High TyG & High UACR group continued to show statistically significant associations (CVD: HR = 1.972, 95% CI: 1.238–3.142, $P = 0.004$; CHD: HR = 2.044, 95% CI: 1.121–3.735, $P = 0.020$; stroke: HR = 2.184, 95% CI: 1.269–3.758, $P = 0.005$). In contrast, neither the High TyG & Medium UACR group nor the High TyG & Low UACR group showed any statistically significant association. Furthermore, the results remained consistent after accounting for competing risks of death from other causes and excluding events occurring within the first two years of follow-up, thereby further supporting the stability of the study conclusions.

E-value sensitivity analysis further supported the robustness of the findings. The E-values for the High TyG & High UACR group were 4.075 for CVD, 4.802 for CHD, and 4.696 for stroke. For the High TyG & Low UACR group, E-values were 3.075 for CVD and 3.021 for stroke, and for the High TyG & Medium UACR group, the E-value was 3.037 for CVD. All E-values exceeded the commonly accepted robustness threshold of 1.82 [38], underscoring the reliability and robustness of the observed associations.

Mutual mediation analyses

The potential bidirectional mediation pathways between the TyG index and UACR in the development of CVD events are illustrated in Fig. 4. For CVD, the total effect of UACR was significant (Total effect = – 10.232, $P < 0.001$), with an ADE of – 9.091 ($P < 0.001$) and an ACME of – 1.141 ($P < 0.001$). The proportion of mediation explained by TyG index was 11.2% ($P < 0.001$) (Fig. 4A). Similarly, the total effect of TyG index on CVD was also significant (Total effect = – 1228.900, $P < 0.001$), with an ADE of – 1172.700 ($P < 0.001$) and an ACME of – 56.267 ($P < 0.001$), with UACR contributing to 4.9% ($P < 0.001$) of the mediation (Fig. 4B). This pattern of bidirectional mediation was consistently observed across different cardiovascular outcomes. For CHD (Fig. 4C-D), the mediation proportions were 12.5% ($P < 0.001$) for the TyG index and 4.4% ($P < 0.001$) for UACR. For stroke (Fig. 4E-F), the corresponding mediation proportions were 9.5% ($P < 0.001$) and 5.9% ($P < 0.001$), respectively. Overall, these results suggest that TyG index explains over 9% of the relationship between UACR and cardiovascular events, while UACR explains more than 4% of the relationship between TyG index and cardiovascular events.

Discussion

In this prospective cohort study based on 14,481 participants with normal-range UACR, we found that both elevated TyG index and UACR were significantly associated with an increased risk of incident CVD event. RCS analysis revealed a non-linear relationship between the TyG index and the risks of overall CVD and stroke, while an approximately linear association was observed with CHD. In comparison, UACR consistently demonstrated a

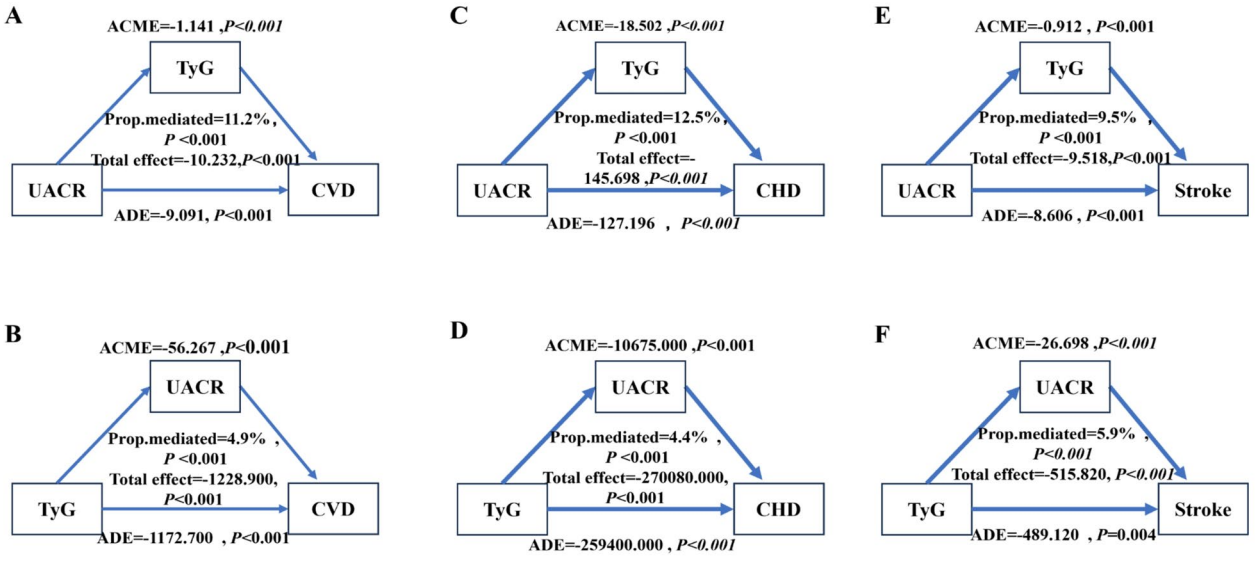


Fig. 4 Mutual mediation analysis of the triglyceride glucose (TyG) index and urinary albumin-to-creatinine ratio (UACR) on cardiovascular diseases(CVD), coronary heart disease(CHD) and stroke.

TyG: triglyceride glucose; UACR: urinary albumin-to-creatinine ratio; CVD: cardiovascular disease; CHD: coronary heart disease; Models were adjusted for age, gender, income level, education level, city, region, marital status, somking, drinking, physical activity, diet, family history of cardiovascular disease. ACME: Average Causal Mediation Effect (indirect effect); ADE: Average Direct Effect; Total Effect: The sum of ACME and ADE; Panels A, C, E display the mediation effects of TyG on the relationship between the UACR index and CVD (**A**), CHD (**C**), and stroke (**E**). Panels B, D,F display the mediation effects of UACR on the relationship between the TyG index and CVD (**B**), CHD (**D**), and stroke (**F**)

linear positive correlation with the risks of CVD, CHD, and stroke. A significant joint effect of TyG index and UACR on CVD incidence was observed. Specifically, compared with the reference group (Low TyG & Low UACR), individuals with concurrently High TyG & High UACR (within the normal range) exhibited significantly increased risks of incident CVD, CHD, and stroke. Notably, even those with High TyG & Low UACR also showed elevated risks of CVD and stroke. while in contrast, the group with High TyG & Medium UACR was associated with an increased risk of CVD only. Moreover, incorporating the joint TyG index and UACR measure significantly improved the incremental predictive value for CVD events. In mediation analyses, an elevated TyG index accounted for 11.2%, 12.5%, and 9.5% of the risks of incident CVD, CHD and stroke, respectively, while an elevated UACR mediated 4.9%, 4.4%, and 5.9% of the corresponding risks. Collectively, these findings underscore the potential clinical value of combined TyG index and UACR monitoring in refining cardiovascular disease prevention strategies among adults in adults with normal UACR level.

TyG index is a well-established, simple surrogate marker for IR. Recent studies have further confirmed its significant association with adverse cardiovascular events in both general and specific disease populations [39–41]. However, evidence regarding this association specifically in individuals with normal renal function remains limited. Although two recent studies in populations with chronic kidney disease or diabetic kidney disease found a significant association between the TyG index and CVD mortality [17, 26], they focused solely on fatal events and involved participants with renal impairment. Furthermore, studies suggest that individuals with a UACR within the normal range may still be at risk of microvascular damage [42, 43]. Therefore, based on data from 14,481 participants with normal UACR, this study systematically evaluated the long-term association between the TyG index and incident cardiovascular events. The results confirmed that a higher TyG groups was significantly associated with an increased risk of incident cardiovascular events, thereby extending the applicability of the TyG index to a broader population for cardiovascular risk assessment. Sensitivity analyses supported the robustness of this finding. In terms of CHD, although the primary model indicated an association between a high TyG index and CHD consistent with previous reports, the difference in CHD risk of the high TyG groups was not statistically significant after adjustment for potential mediators, including BMI, central obesity, dyslipidemia, diabetes, and hypertension [41, 44]. However, RCS analysis and per–1-SD increase in continuous TyG still revealed a significant association. This discrepancy may be attributed to two factors: First, the limited number of CHD events reduced statistical power, making results sensitive to model adjustments; Second,

controlling for mediators might have attenuated the total effect of TyG. The persistent association observed in RCS and continuous analyses implies an underlying biological link between TyG and CHD. Thus, further large-scale cohort studies are needed to clarify this relationship. For stroke, previous studies have reported inconsistent conclusions across different populations [15, 45, 46]. In this study, High TyG group was significantly associated with increased stroke risk among adults aged 18–70 years with normal UACR, and sensitivity analyses yielded consistent results. This may be attributed to the relatively large number of stroke cases and sufficient follow-up time in our cohort, suggesting the TyG index could serve as a useful indicator for stroke risk management in this population. RCS analysis further revealed a non-linear relationship between the TyG index and the risks of incident stroke and overall CVD, consistent with the report by Liu Kun et al. [40] in patients with chronic kidney disease stages 0–3. These findings suggest that IR might exert a threshold effect on stroke risk, where the impact becomes more pronounced once the TyG index exceeds a certain critical value. In contrast, its association with CHD showed an approximately linear dose-response relationship, consistent with the pattern observed in metabolically normal individuals with CKD stages 0–3 [40]. This may suggest that the TyG index have a unique effect on early-stage CHD risk assessment. However, the limited number of cases in the current study necessitates cautious interpretation.

The UACR is a sensitive indicator of early renal impairment [6, 7, 47]. Notably, even within the normal range, elevated UACR has been increasingly recognized as a risk indicator for CVD [48]. Studies across diverse populations—including the general public, diabetic patients, and individuals with fatty liver disease—have consistently linked higher normal-range UACR levels to atherosclerosis, arterial wall thickening, and increased CVD mortality [27, 49–53]. Despite this evidence, most prior research has focused on CVD mortality or intermediate vascular markers rather than incident cardiovascular events. To our knowledge, only one study, conducted in a diabetic population, has examined the association between normal-range UACR and incident heart failure, reporting a positive relationship [48]. However, that study was limited by its moderate sample size (n = 9,287), restriction to a specific disease group, and narrow focus on a single cardiovascular outcome. To address these limitations, our study investigated the association between increasing UACR within the normal range and the risk of incident cardiovascular events (including CHD and stroke) in an adult population aged 18–70 years with normal UACR levels. In fully adjusted models, a continuous increase in UACR was significantly associated with a higher risk of total cardiovascular events. This positive association was further corroborated by a comparison of extreme groups: participants in the high UACR tertile exhibited a significantly elevated risk of total cardiovascular events compared to those in the low UACR tertile. RCS analysis revealed a linear dose-response relationship between UACR and the risks of total CVD, CHD, and stroke individually. It is noteworthy, however, that in the categorical analysis based on tertiles, the risk differences for the individual endpoints of CHD and stroke between the High and Low UACR groups did not reach statistical significance. This discrepancy is likely attributable to the reduced statistical power when dividing the data into categories and testing specific outcomes separately, a limitation that the more powerful continuous RCS analysis was able to overcome. Consequently, the consistent linear trend observed across analytical methods supports a genuine correlation between UACR and cardiovascular risk. The underlying mechanism for this association may involve early subclinical renal impairment. Even at levels below 30 mg/g, a mildly elevated UACR might promote microvascular damage and systemic inflammation, thereby accelerating atherosclerosis and ultimately increasing the risk of cardiovascular events.

Emerging evidence suggests a synergistic effect between IR and renal dysfunction on cardiovascular disease risk. For instance, a study of middle-aged and older Chinese adults showed that participants with a TyG index ≥ 8.6 and an eGFR < 60 ml/min/1.73 m^2 had a significantly higher CVD risk compared to those with a TyG index < 8.6 and eGFR ≥ 60 ml/min/1.73 m^2 (HR = 1.87, 95% CI: 1.13–3.07) [18]. Another study, using data from the NHANES 2009–2018, indicated a significant interaction between the TyG index and CKD status concerning CVD mortality [17]. However, the existing evidence has notable limitations. On one hand, these studies primarily focus on populations with renal dysfunction defined by eGFR, leaving a gap regarding the vast population with a normal UACR (UACR ≤ 30 mg/g). On the other hand, their endpoints are often composite cardiovascular events or CVD mortality, lacking in-depth analysis of specific subtypes like CHD and stroke. This study systematically analyzed the joint effect of TyG and UACR on composite CVD outcomes, as well as CHD and stroke separately, specifically within a population exhibiting normal UACR levels. The findings revealed that the High TyG (>8.823) was consistently associated with an increased risk of composite CVD and stroke across different UACR strata, aligning with trends observed in general populations and further confirming the TyG index's utility as a universal predictor of cardiovascular risk. More importantly, a significantly elevated risk of CVD and stroke was specifically observed among individuals in the highest tertile for both TyG (>8.823) and UACR (>2.373 mg/g). This suggests that even within

the normal UACR range, belonging to the top UACR tertile or having a higher TyG index may independently or synergistically heighten the risk of CVD and stroke [53]. Notably, a significant association between the highest TyG tertile and CHD risk was observed only in the medium UACR group, with no similar trend in the low or high UACR strata. This finding differs from some reports in populations such as those with metabolic dysfunction-associated fatty liver disease [15]. The discrepancy may stem from several factors. Firstly, the limited number of incident CHD cases constrained statistical power. Secondly, the relatively young average age and generally low baseline UACR levels of our study population suggest that most cardiovascular damage was likely at a subclinical stage, where minimal risk accumulation might not yet be sufficient to drive observable CHD events.

It is noteworthy that although traditional multiplicative and additive interaction analyses did not reveal statistically significant interactions, the combined analysis of TyG index and UACR showed that individuals possessing both High TyG and High UACR exhibited the highest risk for composite CVD (including CHD and stroke). This risk was even greater than that observed in individuals having only one of these high-risk factors. This finding remained robust after adjusting for competing risks, excluding events occurring within the first two years of follow-up, and further controlling for eGFR and other potential mediating factors. E-value analysis also supported the reliability of this association. This suggests that the TyG index and UACR may increase CVD risk through partially independent or overlapping pathways, rather than through a mutually amplifying effect. The specific mechanisms require further investigation. Further analysis showed that the associations of the High TyG & Medium UACR and High TyG & Low UACR groups with CVD and stroke were attenuated after adjusting for mediator factors like hypertension and diabetes, while results from other sensitivity analyses aligned with the main model. This suggests that such metabolic factors might also act as mediating pathways for the joint effect of TyG and UACR even in normoalbuminuric populations, partially attenuating their combined impact—a mechanism that warrants further validation in larger studies. Furthermore, subgroup analyses examining the association between the combined TyG & UACR indicator and the incidence of CVD and stroke revealed no significant effect modification by factors such as age, sex, or lifestyle. In subgroups with hypertension or diabetes, no significant impact of High TyG & High UACR on CVD and stroke risk was observed—a finding inconsistent with results from previous studies examining TyG or UACR individually [49, 54, 55]. This inconsistency is likely attributable to the limited number of patients within these specific subgroups, leading to reduced statistical power after stratification. Subgroup analysis for CHD was not performed due to an insufficient number of incident cases. Although findings in certain subgroups and underlying mediating mechanisms require further clarification, the overall results support the potential clinical value of combining the TyG index and UACR for cardiovascular risk stratification in populations with normal UACR.

Regarding the assessment of predictive ability for CVD risk, previous studies have shown that incorporating UACR improves the prediction of heart failure in type 2 diabetic populations [56]. Other research indicates that the TyG index enhances the identification of CVD incidence and mortality risk in diabetic populations [57] and high-risk groups with CKD stages 0–3 [40]. Furthermore, studies combining the TyG index with obesity-related indicators have also demonstrated improved predictive performance for CVD [15, 36, 40]. Our study therefore explored the predictive value of the TyG index and UACR, both individually and in combination, for CVD events in normal UACR level population. It is noteworthy that using the TyG index alone in our study did not significantly enhance CVD prediction, a finding inconsistent with studies conducted in general or chronic kidney disease populations [17]. This discrepancy may be related to the heterogeneous performance of the TyG index across different populations. For instance, some studies suggest the TyG index is more advantageous for predicting the severity of coronary artery stenosis in non-diabetic patients [58], indicating its sensitivity might be limited in populations with normal UACR. Combining TyG with UACR effectively enhanced its overall predictive capability. Although the improvements in the IDI, C-index, and NRI were modest, this still suggests that the combined indicator is particularly useful for identifying high-risk subgroups that might be missed by conventional risk factors alone.

This study extends the existing evidence on the relationship between IR and UACR. Although previous research suggests that renal impairment, marked by reduced eGFR, might mediate approximately 30% of the association between the TyG index and CVD in general populations [18], the eGFR metric used has limited sensitivity for early renal microvascular damage. Given that elevated UACR within the normal range remains a sensitive indicator of early renal microvascular injury [50], this study exploratively analyzed the bidirectional mediation effects between the TyG index and UACR in a normoalbuminuric population. The results indicated that elevated UACR mediated a significant proportion (more than 9.5%) of the association between the TyG index and CVD events (CHD or stroke). Conversely, an elevated TyG index mediated a significant proportion (more than 4.4%) of the association between UACR and CVD events (CHD

or stroke), revealing an intrinsic link between these two factors in CVD pathogenesis. It must be noted that since both UACR and the TyG index were measured cross-sectionally at baseline, the temporal sequence is limited, potentially affecting the inference of the mediation pathway direction. Meanwhile, the relatively small mediation proportions observed may reflect shared metabolic pathways or residual confounding rather than direct causal mechanisms. Therefore, the mediation effects revealed by these findings require validation through future prospective studies with repeated measurements of exposures and mediators at multiple time points to clarify whether these associations represent genuine causal pathways.

Although the precise mechanistic pathways through which elevated TyG index and UACR within their normal ranges interact to influence incident CVD risk are not fully elucidated, growing evidence suggests that even a mild elevation in UACR at the high end of the normal range indicates renal microvascular damage and systemic endothelial dysfunction [59]. These changes are believed to promote atherosclerosis and exacerbate IR [25]. As a reliable surrogate marker of IR, the TyG index contributes to vascular endothelial damage through mechanisms involving lipotoxicity and oxidative stress. This endothelial damage reduces nitric oxide bioavailability and increases vascular permeability, ultimately leading to glomerular filtration barrier impairment and atherosclerotic plaque formation [10, 24, 60]. These two factors act synergistically, creating a vicious cycle that accelerates the progression of atherosclerosis.

To our knowledge, this is the first study to systematically investigate the joint effect of the TyG index and UACR on incident CVD in a population with normal UACR, establish the incremental predictive value of their combination, and conduct an in-depth analysis of their bidirectional mediation effects. The strengths of this study include its prospective cohort design and the use of morning urine samples for UACR measurement, enhancing result stability. However, several limitations persist. First, as the study population was restricted to adults aged 18 and above from Shandong Province, the generalizability of our findings may be limited. Second, although we adjusted for multiple potential confounders, residual confounding due to unmeasured factors (e.g., lack of HbA1c data, which may affect the definition of diabetes) cannot be excluded given the observational design. Third, variables such as medical history, family history, smoking, and alcohol consumption were self-reported and subject to recall bias. Fourth, risk thresholds for the TyG index and UACR within the normal range are not standardized, and furthermore, the TyG index exhibits a nonlinear association with CVD. Consequently, our use of tertiles for grouping might not fully capture the risk gradient associated with their continuous changes. Fifth, the limited number of CHD events may affect the stability of related findings, requiring cautious interpretation. Sixth, the TyG index and UACR data used in the bidirectional mediation analysis came from the baseline survey, precluding the establishment of a strict temporal sequence; thus, inferences about mediation effects need future validation. Seventh, in subgroup analyses, the numerous combined indicator groups led to a small number of outcome events in some subgroups, potentially resulting in unstable estimates. Finally, the TyG index and UACR were measured only at baseline, failing to capture the potential impact of their dynamic changes over time on cardiovascular risk.

Conclusions

In this cohort study of Chinese with normal-range UACR, both TyG index and UACR were associated with incident CVD. Individuals concurrently exhibiting a high TyG(> 8.823) and a high UACR (> 2.373 mg/g but ≤ 30 mg/g) faced the highest risk. Furthermore, the combined TyG index and UACR indicator improved the predictive performance for CVD events. The study also suggested potential bidirectional mediation effects between the TyG index and UACR on CVD risk. These findings highlight the value of combining TyG index and UACR for refined risk stratification in populations with normal-range UACR, which may facilitate targeted interventions for CVD risk management in the future.

Abbreviations

BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
CVD	Cardiovascular disease
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
ESC	European society of cardiology
FPG	Fasting plasma glucose
HbA1c	Hemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HOMA	Homeostasis model assessment
HR	Hazard ratio
ICD-10	International classification of diseases, 10th revision
IQR	Interquartile range
IR	Insulin resistance
LDL-C	Low-density lipoprotein cholesterol
NHANES	National health and nutrition examination survey
RCS	Restricted cubic splines
SD	Standard deviation
SMASH	Shandong-MOH action on salt and hypertension
TC	Total cholesterol
TG	Triglycerides
TyG	Triglyceride-glucose Index
UACR	Urinary albumin-to-creatinine ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-03009-8.

Supplementary Material 1

Acknowledgements
We thank all participants and staff from the SMASH study.

Author contributions
GXL, WJ, and MJX conceived and designed the research. DFJ performed the data analysis and wrote the manuscript. DFJ and GXL interpreted the analyzed results. TJL, LZL, CXR, ZJY, XJW, and ZBY were responsible for the field investigation. DJ, RJ, XCX, and GCC were responsible for data curation. All authors have read and agreed to the published version of the manuscript.

Funding
This research was funded by the Shandong Provincial Salt and Hypertension Prevention and Control Intervention Project from the Chinese Center for Disease Control and Prevention, grant number 1311400010601 and the Provincial Technical Development Plan Grant, grant number 2012GSF11828.

Data availability
The data that support the findings of this study are available from the corresponding author.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and approved by the Preventive Medicine Ethics Committee of Shandong Provincial Centre for Disease Control and Prevention (approval number 2016-7 from 29 April 2016), Prior to participation, all participants provided informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]School of Public Health, Cheeloo College of Medicine, Shandong University, Jinan 250100, China
[2]The Department for Chronic and Non-Communicable Disease Control and Prevention, Shandong Center for Disease Control and Prevention, Jinan 250014, China
[3]National Center for Chronic and Noncommunicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 100050, China
[4]Shandong Provincial Chronic Disease Hospital (Shandong Provincial Rehabilitation Center), Qingdao 266071, China

Received: 15 September 2025 / Accepted: 4 November 2025
Published online: 28 November 2025

References

1. Cardiovascular diseases [Internet]. [cited 2025 Sept 9]. https://www.who.int/health-topics/cardiovascular-diseases#tab=tab_1. Accessed 9 Sept 2025.
2. Zhao D, Liu J, Wang M, Zhang X, Zhou M. Epidemiology of cardiovascular disease in china: current features and implications. Nat Rev Cardiol. 2019;16:203–12. https://doi.org/10.1038/s41569-018-0119-4.
3. Leong DP, Yusuf R, Iqbal R, Avezum Á, Yusufali A, Rosengren A, et al. The burden of cardiovascular events according to cardiovascular risk profile in adults from high-income, middle-income, and low-income countries (PURE): a cohort study. Lancet Global Health. 2025;13:e1406–14. https://doi.org/10.1016/S2214-109X(25)00155-X.
4. Bartz SK, Caldas MC, Tomsa A, Krishnamurthy R, Bacha F. Urine albumin-to-creatinine ratio: a marker of early endothelial dysfunction in youth. [cited 2025 Sept 13]; https://doi.org/10.1210/JC.2015-2230
5. Levey AS, Eckardt K-U, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from kidney disease: improving global outcomes (KDIGO). Kidney Int. 2005;67:2089–100. https://doi.org/10.1111/j.1523-1755.2005.00365.x.
6. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, et al. 2021 ESC guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2021;42:3227–337. https://doi.org/10.1093/eurheartj/ehab484.
7. Hallan SI, Matsushita K, Sang Y, Mahmoodi BK, Black C, Ishani A, et al. Age and the association of kidney measures with mortality and End-Stage renal disease. JAMA. 2012;308:2349–60. https://doi.org/10.1001/jama.2012.16817.
8. Inoue K, Streja E, Tsujimoto T, Kobayashi H. Urinary albumin-to-creatinine ratio within normal range and all-cause or cardiovascular mortality among U.S. Adults enrolled in the NHANES during 1999–2015. Ann Epidemiol. 2021;55:15–23. https://doi.org/10.1016/j.annepidem.2020.12.004.
9. Sung K, Ryu S, Lee J, Lee SH, Cheong E, Hyun Y, et al. Urine Albumin/Creatinine ratio below 30 mg/g is a predictor of incident hypertension and cardiovascular mortality. J Am Heart Assoc. 2016;5:e003245. https://doi.org/10.1161/JAHA.116.003245.
10. Marassi M, Fadini GP. The cardio-renal-metabolic connection: a review of the evidence. Cardiovasc Diabetol. 2023;22:195. https://doi.org/10.1186/s12933-023-01937-x.
11. Hill MA, Yang Y, Zhang L, Sun Z, Jia G, Parrish AR et al. Insulin resistance, cardiovascular stiffening and cardiovascular disease. Metabolism - Clinical and Experimental [Internet]. Elsevier; 2021 [cited 2024 Sept 21];119. https://doi.org/10.1016/j.metabol.2021.154766
12. Gastaldelli A. Measuring and estimating insulin resistance in clinical and research settings. Obes (Silver Spring). 2022;30:1549–63. https://doi.org/10.1002/oby.23503.
13. Tahapary DL, Pratisthita LB, Fitri NA, Marcella C, Wafa S, Kurniawan F, et al. Challenges in the diagnosis of insulin resistance: focusing on the role of HOMA-IR and Tryglyceride/glucose index. Diabetes Metabolic Syndrome: Clin Res Reviews. 2022;16:102581. https://doi.org/10.1016/j.dsx.2022.102581.
14. Liu C, Liang D, Xiao K, Xie L. Association between the triglyceride–glucose index and all-cause and CVD mortality in the young population with diabetes. Cardiovasc Diabetol. 2024;23:171. https://doi.org/10.1186/s12933-024-02269-0.
15. Qiao Y, Wang Y, Chen C, Huang Y, Zhao C. Association between triglyceride-glucose (TyG) related indices and cardiovascular diseases and mortality among individuals with metabolic dysfunction-associated steatotic liver disease: a cohort study of UK biobank. Cardiovasc Diabetol. 2025;24:12. https://doi.org/10.1186/s12933-024-02572-w.
16. Chen J, Wu K, Lin Y, Huang M, Xie S. Association of triglyceride glucose index with all-cause and cardiovascular mortality in the general population. Cardiovasc Diabetol. 2023;22:320. https://doi.org/10.1186/s12933-023-02054-5.
17. Qin Y, Xuan L, Deng Y, Wang F, Liu B, Wang S. Triglyceride-glucose index and mortality risk in individuals with or without chronic kidney disease: insights from a National survey of united States adults, 1999–2018. Nutrition, metabolism and cardiovascular diseases. Volume 34. Elsevier; 2024. pp. 1994–2001. https://doi.org/10.1016/j.numecd.2024.04.003.
18. Cui C, Liu L, zhang T, Fang L, Mo Z, Qi Y, et al. Triglyceride-glucose index, renal function and cardiovascular disease: a National cohort study. Cardiovasc Diabetol. 2023;22:325. https://doi.org/10.1186/s12933-023-02055-4.
19. Ren X, Jiang M, Han L, Zheng X. Association between triglyceride-glucose index and chronic kidney disease: a cohort study and meta-analysis. Nutr Metabolism Cardiovasc Dis. 2023;33:1121–8. https://doi.org/10.1016/j.numecd.2023.03.026.
20. Cersosimo E, DeFronzo RA. Insulin resistance and endothelial dysfunction: the road map to cardiovascular diseases. [cited 2025 Sept 14]; https://doi.org/10.1002/dmrr.634
21. Ochodnicky P, Henning RH, Van Dokkum RPE, De Zeeuw D. Microalbuminuria and endothelial dysfunction: emerging targets for primary prevention of End-organ damage. J Cardiovasc Pharmacol. 2006;47:S151–62. https://doi.org/10.1097/00005344-200606001-00009.
22. Li M, Ji R, Li Z, Zhao S, Liu R, Liu X, et al. Impact of metabolic abnormalities on the association between normal-range urinary albumin-to-creatinine ratio and cardiovascular mortality: evidence from the NHANES 1999–2018. Diabetol Metab Syndr. 2024;16:250. https://doi.org/10.1186/s13098-024-01488-5.
23. Gu S, Wang A, Ning G, Zhang L, Mu Y. Insulin resistance is associated with urinary albumin-creatinine ratio in normal weight individuals with hypertension and diabetes: the REACTION study. J Diabetes. 2020;12:406–16. https://doi.org/10.1111/1753-0407.13010.

24. Davignon J, Ganz P. Role of endothelial dysfunction in atherosclerosis. Circulation [Internet]. Lippincott Williams & Wilkins; 2004. https://doi.org/10.1161/01.CIR.0000131515.03336.f8. [cited 2025 Sept 13].
25. Muniyappa R, Sowers JR. Role of insulin resistance in endothelial dysfunction. Rev Endocr Metab Disord. 2013;14:5–12. https://doi.org/10.1007/s11154-012-9229-1.
26. Penno G, Solini A, Orsi E, Bonora E, Fondelli C, Trevisan R, et al. Insulin resistance, diabetic kidney disease, and all-cause mortality in individuals with type 2 diabetes: a prospective cohort study. BMC Med. 2021;19:66. https://doi.org/10.1186/s12916-021-01936-3.
27. Bartz SK, Caldas MC, Tomsa A, Krishnamurthy R, Bacha F. Urine albumin-to-creatinine ratio: a marker of early endothelial dysfunction in youth. J Clin Endocrinol Metab. 2015;100:3393–9. https://doi.org/10.1210/JC.2015-2230.
28. Salmon AH, Satchell SC. Endothelial glycocalyx dysfunction in disease: albuminuria and increased microvascular permeability. J Pathol. 2012;226:562–74. https://doi.org/10.1002/path.3964.
29. Mahemuti N, Zou J, Liu C, Xiao Z, Liang F, Yang X. Urinary albumin-to-creatinine ratio in normal range, cardiovascular Health, and all-cause mortality. Jama Netw Open. 2023;6:e2348333. https://doi.org/10.1001/jamanetworkopen.2023.48333.
30. Xu A, Ma J, Guo X, Wang L, Wu J, Zhang J, et al. Association of a Province-Wide intervention with salt intake and hypertension in Shandong Province, China, 2011–2016. Jama Intern Med. 2020;180:877. https://doi.org/10.1001/jamainternmed.2020.0904.
31. Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Dennison Himmelfarb C et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the american college of cardiology/american heart association task force on clinical practice guidelines. Hypertension. American Heart Association; 2018;71:1269–324. https://doi.org/10.1161/HYP.0000000000000066
32. Chinese Elderly Type 2 Diabetes Prevention and Treatment of Clinical Guidelines Writing Group, Geriatric Endocrinology and Metabolism Branch of Chinese Geriatric Society, Geriatric Endocrinology and Metabolism Branch of Chinese Geriatric Health Care Society, Geriatric Professional Committee of Beijing Medical Award Foundation, National Clinical Medical Research Center for Geriatric Diseases (PLA General Hospital). [clinical guidelines for prevention and treatment of type 2 diabetes mellitus in the elderly in China (2022 edition)]. Zhonghua Nei Ke Za Zhi. 2022;61:12–50. https://doi.org/10.3760/cma.j.cn112138-20211027-00751.
33. Wang C, Lu Z, Zhang J, Chen X, Xu J, Zhang B, et al. The relationship between Low-Sodium salt intake and both blood pressure level and hypertension in Chinese residents. Nutrients. 2024;16:1909. https://doi.org/10.3390/nu16121909.
34. CKD-EPI creatinine Eq. (2021) | national kidney foundation [Internet]. [cited 2025 Sept 13]. https://www.kidney.org/ckd-epi-creatinine-equation-2021-0. Accessed 13 Sept 2025.
35. Zhang Y-B, Chen C, Pan X-F, Guo J, Li Y, Franco OH, et al. Associations of healthy lifestyle and socioeconomic status with mortality and incident cardiovascular disease: two prospective cohort studies. BMJ (clin Res Ed). 2021;373:n604. https://doi.org/10.1136/bmj.n604.
36. Xia X, Chen S, Tian X, Xu Q, Zhang Y, Zhang X, et al. Association of triglyceride-glucose index and its related parameters with atherosclerotic cardiovascular disease: evidence from a 15-year follow-up of Kailuan cohort. Cardiovasc Diabetol. 2024;23:208. https://doi.org/10.1186/s12933-024-02290-3.
37. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med Am Coll Physicians. 2017;167:268–74. https://doi.org/10.7326/M16-2607.
38. Sjölander A, Greenland S. Are E-values too optimistic or too pessimistic? Both and neither! Int J Epidemiol. 2022;51:355–63. https://doi.org/10.1093/ije/dyac018.
39. Liu X, Tan Z, Huang Y, Zhao H, Liu M, Yu P, et al. Relationship between the triglyceride-glucose index and risk of cardiovascular diseases and mortality in the general population: a systematic review and meta-analysis. Cardiovasc Diabetol. 2022;21:124. https://doi.org/10.1186/s12933-022-01546-0.
40. Liu K, Hu J, Huang Y, He D, Zhang J. Triglyceride-glucose-related indices and risk of cardiovascular disease and mortality in individuals with cardiovascular–kidney–metabolic (CKM) syndrome stages 0–3: a prospective cohort study of 282,920 participants in the UK biobank. Cardiovasc Diabetol. 2025;24:277. https://doi.org/10.1186/s12933-025-02842-1.
41. Che B, Zhong C, Zhang R, Pu L, Zhao T, Zhang Y, et al. Triglyceride-glucose index and triglyceride to high-density lipoprotein cholesterol ratio as potential cardiovascular disease risk factors: an analysis of UK biobank data. Cardiovasc Diabetol. 2023;22:34. https://doi.org/10.1186/s12933-023-01762-2.
42. Bull Rasmussen IK, Skriver-Moeller A-C, Ripa RS, Hasbak P, Wasehuus VS, Hadji-Turdeghal K, et al. Increased subclinical coronary artery pathology in type 2 diabetes with albuminuria. Diabetes. 2024;73:490–6. https://doi.org/10.2337/db23-0529.
43. Upadhyayula SK, Ubaru S, Raajeshwi P, Ajavindu CN, Rao AB. Neutrophil-lymphocyte ratio and urine albumin-creatinine ratio as indicators of microvascular complications in type 2 diabetes mellitus: a cross-sectional study. Cureus. 2024;16:e75196. https://doi.org/10.7759/cureus.75196.
44. Jia Y, Zhang S, Liu J. Exploring bmi's mediating influence on cardiovascular risk correlations with the triglyceride-glucose index: using NHANES and CHARLS cohorts. Front Cardiovasc Med. 2025;12:1593413. https://doi.org/10.3389/fcvm.2025.1593413.
45. Li F, Wang Y, Shi B, Sun S, Wang S, Pang S, et al. Association between the cumulative average triglyceride glucose-body mass index and cardiovascular disease incidence among the middle-aged and older population: a prospective nationwide cohort study in China. Cardiovasc Diabetol. 2024;23:16. https://doi.org/10.1186/s12933-023-02114-w.
46. Jiang Y, Shen J, Chen P, Cai J, Zhao Y, Liang J, et al. Association of triglyceride glucose index with stroke: from two large cohort studies and Mendelian randomization analysis. Int J Surg (lond Engl). 2024;110:5409–16. https://doi.org/10.1097/JS9.0000000000001795.
47. Tao J, Sang D, Zhang X, Liu X, Wang G, Chen S, et al. An elevated urinary albumin-to-creatinine ratio increases the risk of incident cardia-cerebrovascular disease in individuals with type 2 diabetes. Diabetol Metab Syndr. 2024;16:30. https://doi.org/10.1186/s13098-024-01256-5.
48. Xu J, Knowler WC, Devereux RB, Yeh J, Umans JG, Begum M, et al. Albuminuria within the normal range and risk of cardiovascular disease and death in American indians: the strong heart study. Am J Kidney Dis. 2007;49:208–16. https://doi.org/10.1053/j.ajkd.2006.10.017.
49. Pang X, Dan W, Lin L, Li H, Rao X, Li S. Association of normal range of urinary albumin-to-creatinine ratio with all-cause mortality among diabetic adults with preserved kidney function: national health and nutrition examination survey (NHANES) 2003–2018. Diabetes Obes Metab. 2025;27:2670–8. https://doi.org/10.1111/dom.16269.
50. Xie X, Peng Z, Li H, Li D, Tu Y, Bai Y et al. Association of Urine Albumin/Creatinine Ratio below 30 mg/g and Left Ventricular Hypertrophy in Patients with Type 2 Diabetes. Cangemi R, editor. BioMed Res Int. 2020;2020:5240153. https://doi.org/10.1155/2020/5240153
51. Lin X, Song W, Zhou Y, Gao Y, Wang Y, Wang Y, et al. Elevated urine albumin creatinine ratio increases cardiovascular mortality in coronary artery disease patients with or without type 2 diabetes mellitus: a multicenter retrospective study. Cardiovasc Diabetol. 2023;22:203. https://doi.org/10.1186/s12933-023-01907-3.
52. Kweon S-S, Shin M-H, Lee Y-H, Choi J-S, Nam H-S, Park K-S, et al. Higher normal ranges of urine albumin-to-creatinine ratio are independently associated with carotid intima-media thickness. Cardiovasc Diabetol. 2012;11:112. https://doi.org/10.1186/1475-2840-11-112.
53. Li M-F, Tu Y-F, Li L-X, Lu J-X, Dong X-H, Yu L-B, et al. Low-grade albuminuria is associated with early but not late carotid atherosclerotic lesions in community-based patients with type 2 diabetes. Cardiovasc Diabetol. 2013;12:110. https://doi.org/10.1186/1475-2840-12-110.
54. Zhang Q, Xiao S, Jiao X, Shen Y. The triglyceride-glucose index is a predictor for cardiovascular and all-cause mortality in CVD patients with diabetes or pre-diabetes: evidence from NHANES 2001–2018. Cardiovasc Diabetol. 2023;22:279. https://doi.org/10.1186/s12933-023-02030-z.
55. Wang J, Wang Y, Li Y, Hu Y, Jin L, Wang W, et al. High normal urinary albumin–creatinine ratio is associated with Hypertension, type 2 diabetes Mellitus, HTN with T2DM, dyslipidemia, and cardiovascular diseases in the Chinese population: a report from the REACTION study. Front Endocrinol. 2022;13:864562. https://doi.org/10.3389/fendo.2022.864562.
56. Tao J, Sang D, Zhen L, Zhang X, Li Y, Wang G, et al. Elevated urine albumin-to-creatinine ratio increases the risk of new-onset heart failure in patients with type 2 diabetes. Cardiovasc Diabetol. 2023;22:70. https://doi.org/10.1186/s12933-023-01796-6.
57. Yan L, Zhou Z, Wu X, Qiu Y, Liu Z, Luo L, et al. Association between the changes in the estimated glucose disposal rate and new-onset cardiovascular disease in middle-aged and elderly individuals: a nationwide prospective cohort study in China. Diabetes Obes Metab. 2025;27:1859–67. https://doi.org/10.1111/dom.16179.

58. Darroudi S, Mahdavizadeh V, Mirzaei AH, Esparham A, Ahmadyar S, Esmaily H, et al. Triglyceride glucose index and triglyceride HDL ratio as predictors of coronary artery stenosis in diabetic and non-diabetic patients. Nutr Metab Cardiovasc Dis: NMCD. 2024;34:1692–5. https://doi.org/10.1016/j.numecd.2023.12.001.
59. Huang M-J, Wei R, Zhao J, Su T, Li Q, Yang X, et al. Albuminuria and endothelial dysfunction in patients with non-diabetic chronic kidney disease. Med Sci Monit. 2017;23:4447–53. https://doi.org/10.12659/MSM.903660.
60. Rask-Madsen C, King GL. Mechanisms of disease: endothelial dysfunction in insulin resistance and diabetes. Nat Rev Endocrinol Nat Publishing Group. 2007;3:46–56. https://doi.org/10.1038/ncpendmet0366.

Publisher's note